BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problems Mailbox.

Translation of German Laid Open Patent 1 494 939

TITLE: IMPLANTATION MATERIAL AND METHOD OF MAKING THE SAME

Prothesises made from synthetic material with the assistance of a surgical procedure are used for replacing sickened or nonfunctional arteries. The synthetic prothesises being implanted in the test animal or in the human being must be completely or substantially impermeable for body fluids,so that a seeping of blood or body juices does not occur or remains in tolerable limits after the transplantation. However the insufficient porosity of these synthetic prosthesises prevents an adjustment into the body organism caused by growing around or growing therethrough,so that the functionality to be expected for a long time concerning the synthetic prostehesis cannot be achieved. Prosthesises with a higher porosity,which improve the end result, must be sealed with a suitable material by means of impregnation in order to prevent the danger of acute large loss of blood or liquid. The material for impregnation is to be expected to be compatible with the receiver organism,has to have a mechanical sturdiness,must be primarily insoluble in blood and body juices, however must also be resorbable within a certain span of time by the receiver organism and replaceable by a newly formed tissue.

Methods are already known for impregnating porous synthetic arteries,whereby the impregnation material employed does not meet all the desired requirements. One method uses a water soluble gelatine which is applied in a heated solution onto the synthetic prosthesis by immersing it therein,being dried and denatured by a four hour heating (to 140°C),thus being rendered insoluable. In another method water soluble gelatine is brought to a reaction with a thiol group containing chemical compound,subsequently cross linked by oxydizing the thiol groups into disulfide bridges and thereby changed into a water insoluble form. Moreover,the employment of collagen,an animal protein material, was also described. In this method either general insoluble collagen of animal origin is employed,or a collagen which is severely changed in its natural characteristics due to tanning with different chemicals.

All materials and methods hitherto employed for impregnation have shortcomings which are also disadvantageous during the transplantation on the impregnated synthetic arteries onto a receiver organism,for example. The gelatine is changed by the heat influence or by the chemical linking with a sulfur containing body alien compound in such a manner that harmful reactive effects occur on the receiver organism. The use of general collagen is

disadvantageous that,because of its complete insolubility,it cannot be obtained in a purity degree being required for the impregnation method,so that it causes uncontrollable inflammable or other harmful rejection reactions in the receiver organism after transplantation. Additional treatment with tanning chemicals which have a chemical linking with the collagen renders the collagen into an unnatural alien protein,whose necessary decomposition requires nonphysiological metabolic reactions and the existence thereof prevents the desired tissue forming.

Also disadvantageous in the hitherto known impregnated synthetic prosthesises is the insufficient elasticity of the impregnation material. The inflexible fixing of the impregnation material may cause the danger of a separation during mechanical stress or change its structure,so that before implantation a soaking in acqueous solutions becomes necessary for achieving a sufficient flexibility. The removal of this disadvantage by adding softeners of the known type,for example,mannitol.necessarily results in introducing further body alien substances into the receiver organism.

It is an object by the inventor to prevent the described disadvantageous side effects by a novel method for impregnating the prosthesises.

It is an object of the invention to provide an implantation material,in particular a prosthesis,consisting of a porous body made of a synthetic material being impregnated with a protein like material,characterized in that the impregnation material consists of an acid soluble procollagen.

Procollogen is a component of many human and animal tissues,among others,leather skin and arteries,and therefore represents a physiological replacement material. Procollagen is a protein which can be extracted from the fresh tissue by means of organic acids containing buffers of a hydrogen concentration of ph 3.5 and an ion strength of $\Gamma/2 = 0.2$ in soluble form which during the neutralisation of the solvent or removal of the acid transforms into a quasicrystalline fiberlike water insoluble state. This procedure is reversible. The molecular weight of the dissolved procollagen is 360 000,the rod shaped molecules have a length of 2 800 Å and a diamter of 15 Å. The chemical composition is known. There are no differences in the composition of collagen in mammals.

Moreover,the object of the invention is a method for making the implantation material. For processing the method a 0.1 - 5.o, preferably between 1.o and 1.5 percent by weight acqueous,weak acid solution,whose pH-value is adjusted by a buffer or a weak acid (for example,citrate buffer or acetic acid) is made from purified procollagen,and,if need be,a body compatible softener,for example,glycerine is added depending whether a volatile or non-volatile substance had been employed for dissolving the collagen. If the solution is not immediately employed for impregnation,a slght amount of such a conserving agent may be added for preventing of germ growth,which does not have any protein denaturing characteristics and which volatizes during drying. For this purpose thymol is suitable,for example.

The viscous solution of viscous flowing consistency is applied in a suitable form onto the porous synthetic material,for example, a porous synthetic hoseso that the inner and outer surface of the synthetic hose are covered by a liquid felt which penetrates through the pores of the tissue. The drying is performed under conditions which assures a uniform distribution of the impregnation film. A maximum temperature of 30 - 40^{o}C should not be exeeded,since in this temperature range the thermical conversion of the procollagen into the fiber form is otherwise superimposed by the denaturing process. Depending on the concentration of the dissolved procollagen, or depending on the desired degree of impregnation the process of applying and drying may be made once or a plurality of times.

For converting the procollagen from the dissolved form into the unsoluble form,the acid added to the impregnation solution must be removed. Thereby,as is the case under natural conditions in the living tissue,a directed alignment of theindividual molecules, which are in a disoriented amount in the solution,form into a water insoluble macromolecular fiber like unit.

When using volatile acid substances theacid content reduces with increasing evaporation during the drying of the impregnation solution,while simultaneously the collagen which is maintained in the dissolved form by the acid is converted into the insoluble fibrous form. The softener which already had been added to the solution before the application remains in a uniform distributed form in the impregnation material and keeps it pliable.

When using nonvolatile acids (for example,citric acid) the same must be removed after drying from the impregnation material for converting the procollagen into the unsoluble fiber form. This is performed by applying an acueous solution (for example,0.005-0.1 m Ma_2HPO_4) being buffered at its neutral point on the synthetic body being coated with the impregnation material. For preventing eventual dwell processes a slight amount of an anionic polysaccharide,for example,potassium-chondroitin-4-sulfate or potassiumpolymannurate,or other substances favoring the forming of fibers,for example,ethanol or sodium chloride may be added to the acqueous solution. Subsequently the salts are removed by treatment with distilled water. After a sufficientaction of an acqueous solution containing the softener in a suitable concentration a drying process is subsequently performed.

The method in accordance with the invention will be explained by a few following examples:

Example 1

1.25 g pure procollagen dry substance and 1.0 ml bidistilled glycerine are dissolved in 100 ml 0.1 n acetic acid with the assistance of an homogenizer. The created viscous slightly opal solution is centrifuged for 5 min. at 3000r/min for removing air bubbles and immediately used in the following manner for impregnating of a porous synthetic prosthesis: 5 ml of the impregnation solution are at first uniformly distributed on the inner wall of a 20 cm long knitted hose like and with a bellows provided prosthesis made from polytetrafluorethylene havinga diameter of 10 mm. Thereafter the two ends of the prosthesis are pushed by 1 cm each over a synthetic pipe having the same diameter and fixed in such a manner that the prosthesis is in a horizontal and straight condition. By means of a drive system the system is rotated around the assumed inner longitudinal axis of the prosthesis with a speed of 120 r/min. while applying as much impregnation solution solution uniformly with a hair brush,so that the same is covered by a liquid film. Under a constant rotation,which assures a uniform distribution of the impregnation solution on the inner and outer face,a drying process is performed at 20^{o}. The outer impregnation is repeated four times in the same manner, whereby about 25 ml impregnation solution is consumed. After completion of the last drying process,the prosthesis is released from the fixation position. The treatment results in a poreless

water insoluble impregnation film firmly adhering on the synthetic prosthesis which primarily seals the porous synthetic prosthesis absolutely liquid tight. The longitudinal elasticity of the synthetic pipe obtained by the bellows stamp is substantially maintained after the impregnation. The prosthesis may be briefly heated to about 110°C for the purpose of sterilisation without losing the mentioned characteristics.

Example 2.

1.25 g pure procollagen dry substance are dissolved with the assistance of a homogenizer in 100 ml citrate buffer having the following composition: 1.05 g citronic acid monohydrate,5 ccm n NCl and 10 ccm n NoOH are filled with distilled water to 100 ccm. Before homogenizing 0.1 g thymol is added corresponding to a concentration of o.1%. The impregnation solution is stable for a few weeks when stored cold at + 4°C. The application of the impregnation solution is performed as described in example 1,however with the difference that the hose inner wall is not wetted with impregnation solution,e.i.,the impregnation is only performed from the outside and the drying is performed at 30°C in a filtered air flow. After a five time application and drying of the impregnation solution the impregnated synthetic prothesis is brought, for a complete conversion of the proollagen into the insoluble fibre shape,at +4°C for 48 hours into a o.ol mol Ma_2HPO_4-solution containing 5%NaCl and subsequently for 24 hrs in distilled water for removing the salts and for receiving the softener and a 105 acqueous solution of glycerin. The drying is performed at 20°C. The resulting continuous well adhering impregnation film encompassing the prosthesis like a jacket seals the prosthesis air and liquid tight. The longitudinal elasticity of the prosthesis is not noticeably changed. As in example 1,the prosthesis may be heated to about 110°C for the purpose of sterilisation without losing the mentioned characteristics.

Example 3

Making,plurality of applying and drying of the impregnat solution is performed as in example 2. The conversion of the impregnation material into the water insoluble fiber form is performed in a solution containing 0.15% of the potassium salt of chondroitin-4-sulfate in 0.01 ml acqueous Ma_2HPO_4-solution. The further treatment and the characteristics of the prostesis as in example 2.

Example 4

1.5 g solid procollagen dry substance and 1 ml bidistilled glycerin are homogenized in 100 ml 0.25 n acetic acid and is used for impregnation of a porous synthetic material in the following manner: 20 cm^2 of a 5 mm thick porous synthetic materia are centrifuged in the impregnation solution for 15 min. at 3000 r/min,whereby the air in the pores of the synthetic material is completely removed and replaced by the impregnation solution. The synthetic material which is removed after centrifugation from the impregnation solution contains an amount of impregnation solution corresponding to the pore volume which adhers due to the viscosity of the impregnation solution. After drying at 20°C while occasionally turing,the porous synthetic material will receive the impregnation solution in a uniformly distributed form. The compressability and elasticity of the synthetic materia are maintained.

The subject invention offers the following advantages with respec to the hitherto known methods:
Exlusively physiological substances are used for impregnation which are available after careful preparation while completely maintaining the natural characteristics and highly purefied, and which may be applied in a dissolved form onto the synthetic prosthesis.
During transplantation onto another organism the procollagen is characterized by particular body and tissue compatability and is accepted by the receiver without any reaction and within a certain time span without any adverse tissue or or other reaction actions and disssolved completely

After conversion into the water insoluble form the procollagen has a high elasticity and very good adherence capability on the synthetic material. In light of the mechanical elasticity of the impregnation material the elastic characteristics of the synthetic material are substantially maintained even after the impregnation.
The impregnated implantation material in accordance with the method is suitable in its corresponding shape not only to replace arteries but also for replacing other fluid containing passageways and hollow organs,for example,esophagus,bile duct, bladder and ureter.

CLAIMS

1) Implantation material,in particular prosthesises with a porous body made of synthetic material being impregnated with a protein like material,characterized in that said impregnation material consists of an acid soluble procollagen.

2) Method for making the implantation material in accordance with claim 1,characterized in that an impregnation material consisting of a weak acid o.1 - 5.0 percent by weight acqueous solution of acid soluble purified procollagen is applied on said porous body,dried and for conversion of the acid soluble procollagen into the water insoluble fiber form is relieved from the acid components.

3) Method in accordance with claim 2,characterized in that as the procollagen dissolving component an acqueous solution of a weak volatile acid or a volatile buffer is employed in a concentration adapted to the amount of the procollagen.

4) Method in accordance with claims 2 and 3,characterized in that a body compatible softener is added to said impregnation solution before the application onto said porous body.

5) Method in accordance with claim 2,characterized in that as the procollagen dissolving component a nonvolatile acid buffer or a nonvolatile weak acid in an acqueous solution is used.

6) Method in accordance with claim 2 and 5,characterized in that the implantation material being provided with the impregnation material and dried thereon is brought into an acqueous solution which is buffered at its neutral point for removing nonvolatile components.

7) Method in accordance with claim 2,5 and 6,characterized in that a substance is added to the acqueous solution which is buffered at its neutral point enhancing the conversion of the procollagen into the insoluble fiber shape.

8) Method in accordance with claims 2 - 7,characterized in that said impregnated implantation material being relieved from acid components is brought into an acqueous solution of glycerin.

9) Method in accordance with one of claims 2 - 8,characterized in that a volatile conservation agent is added to said procollagen solution for increasing its stability.